REMARKS

Rejection of Claims 15, 17, 59, 60 and 62-71 Under 35 U.S.C. § 102(e,f) or Alternatively, Under 35 U.S.C. § 103 (Item 3 of Office Action)

Claims 15, 17, 59, 60 and 62-71 have been rejected under 35 U.S.C. § 102(e,f), or alternatively, under 35 U.S.C. § 103, as they are said to be obvious over Stamler *et al.* (US Patent No. 6,471,978). It is assumed that the Examiner means 35 U.S.C. § 102(e) or 35 U.S.C. § 102(f) as alternative theories for anticipation.

Stamler *et al.* (US Patent No. 6,471,978) describe medical devices coated with a nitric oxide adduct. Among the nitric oxide adducts recited for use in the medical devices are S-nitroso-proteins. US Patent No. 6,471,978 describes methods of producing S-nitroso-proteins at column 19, lines 6-19. However, one of ordinary skill in the art would not be able to make and use S-nitroso-hemoglobin or any other form of nitrosated or nitrated hemoglobin based on these described methods. From what is taught in US 6,471,978, one of ordinary skill in the art would have no reason to think that any nitrosated or nitrated form of hemoglobin could be made. Further, no information is given on the stability of any hemoglobin derivative, or on its suitability to being used to treat any medical condition. No person of ordinary skill in the art would be able to carry out any of the methods of Claims 15, 17, 59, 60 and 62-71 by looking for guidance from US Patent No. 6,471,978, as it does not have sufficient teachings regarding hemoglobin for anyone to be able to perform any chemical reaction to make any derivatized form of hemoglobin. Further, US 6,471,978 does not have any experimental evidence regarding the biological activity of hemoglobin that has been nitrosated or nitrated. One of ordinary skill in the art would know that underivatized hemoglobin is a vasoconstrictor. Therefore, one of ordinary skill in the art would would require instruction in not only how to make a hemoglobin derivative that is a vasodilator, but also how to use the hemoglobin derivative. No invention could have been derived from the people named as inventors on US Patent No. 6,471,978, as there is no indication that they ever had possession of sufficient knowledge to produce any derivatives of hemoglobin, or to practice the methods of Claims 15, 17, 59, 60 and 62-71.

One of ordinary skill in the art who studies US Patent No. 6,471,978 might think of hemoglobin as a candidate protein to be modified to a SNO-derivative, because hemoglobin is

mentioned. However, one intending to produce a derivative of hemoglobin with the biological activity required to carry out the methods of Claims 15, 17, 59, 60 and 62-71 would not be able to find a procedure to produce such a derivative -- in US 6,471,978 or in any other publication existing at the time the priority application for the subject application was filed. US Patent No. 6,471,978 does not contain an enabling description of how to make any kind of derivative of hemoglobin -- nitrosated, nitrated, or otherwise. Nothing in the prior art combined with US 6,471,978 makes up for this deficiency. Therefore, the methods of Claims 15, 17, 59, 60 and 62-71 cannot be obvious.

Rejection of Claims 15-17 and 59-71 Under 35 U.S.C. § 102(e,f) or Alternatively, Under 35 U.S.C. § 103 (Item 4 of Office Action)

Claims 15-17 and 59-71 have been rejected under 35 U.S.C. § 102(e,f), or alternatively, under 35 U.S.C. § 103, as they are said to be obvious over Stamler *et al.* (US Patent No. 6,583,113). It is assumed that the Examiner means 35 U.S.C. § 102(e) or 35 U.S.C. § 102(f) as alternative theories for anticipation.

Stamler *et al.* (US Patent No. 6,583,113) has the same content as WO 93/09806, with the exception of the claims. US Patent No. 6,583,113 discloses methods purported to produce S-nitroso-proteins, in particular, S-nitroso-tPA (tPA is tissue plasminogen activator), S-nitroso-BSA (BSA is bovine serum albumin), S-nitroso-cathepsin B, S-nitroso-lipoprotein and S-nitroso-immunoglobulin, and methods for producing the same, using NO or $NaNO_2$ as the reagent under acidic conditions. No data show what structure or biological function any of those proteins might retain after the treatment to derivatize them. They also report a method which they claim results in the synthesis of S-nitroso-hemoglobin. However, this compound was not produced by any method reported in US Patent No. 6,583,113. A Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 mailed to the Patent Office on 2 September 1999 referred to the content of WO 93/09806 in stating that the experiments described therein purporting to produce SNO-hemoglobin failed. Methods purported to synthesize other S-nitroso-proteins, which the experimenters hoped would nitrosate or polynitrosate hemoglobin, dissociated hemoglobin into its subunits, oxidized the heme Fe and rendered the product fragments useless for carrying oxygen. Methods described in the specification that resulted in the synthesis of nitrosated

hemoglobins are substantially different from the unsuccessful acidified nitrite method described in WO 93/09806. The method of Example 19 of US 6,583,113 is incomplete and does not instruct one of ordinary skill in the art in how to produce any compound.

A telephonic interview was held on February 13, 2001, in which the attorney Carol Egner and the inventor Jonathan Stamler discussed issues with the Examiner, Bennett Celsa, in the parent application 08/796,164. Based on the Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 filed on 2 September 1999 and exhibits accompanying the Declaration, the Examiner stated that he accepted that WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin. There remained a question with the Examiner of whether other species of nitrosated hemoglobin could have been produced from methods described in WO 93/09806. It was presented to the Examiner that it would be very unlikely that NO adducts were produced at O, N or C atoms in the hemoglobin molecule, if none could be detected at S atoms, because the thiol groups were the most reactive nucleophilic sites. WO 93/09806 does not present a method to use nitrosylhemoglobin as a donor of NO in therapy. Before the invention by Applicants, nitrosylhemoglobin would not have been expected to be, or to be converted to, a donor of NO. WO 93/09806, and therefore, US 6,583,113 do not present an enabling description of any method to use any nitrosated hemoglobin in therapy. Therefore, there is no basis for this rejection.

There is no evidence presented in US Patent No. 6,583,113 that any form of nitrosated or nitrated hemoglobin has any biological activity that can be applied to any disease or medical condition. There is nothing in US Patent No. 6,583,113 that indicates that any form of nitrated or nitrosated hemoglobin can be produced. Nitrosyl-hemoglobin is only mentioned in column 30, lines 13-17. The experimenters attempted to produce nitrosyl-hemoglobin to use as a standard for comparison of its UV spectrum. No therapeutic qualities of nitrosyl-hemoglobin are discussed or implied in US Patent No. 6,583,113. No person of ordinary skill in the art could infer from the teachings of US Patent No. 6,583,113 that a nitrosated or nitrated hemoglobin could be produced that would be useful in a method of therapy. One of ordinary skill in the art would conclude from Example 19 of 6,583,113 that the synthesis of SNO-hemoglobin failed. Because the applicants listed for US Patent No. 6,583,113 were not the first to invent, and did not have in their possession any invention of a method of treating a disease or medical condition in a

mammal or human patient, comprising administering nitrosated or nitrated hemoglobin, they could not have conveyed any information on an invention to anyone else.

With regard to possible obviousness of the subject matter of Claims 15-17 and 59-71, U.S. 6,583,113 does not teach any physiological effect of a nitrosated or nitrated hemoglobin. U.S. 6,583,113 contains insufficient teaching for one of ordinary skill in the art to conclude that any derivative of hemoglobin was produced. Therefore, it would not be obvious to one of ordinary skill in the art that any nitrosated or nitrated derivative of hemoglobin could be made or that any nitrosated or nitrated derivative of hemoglobin could be used for any effect on platelet activation or adherence.

Rejection of Claims 15, 17, 59-60 and 62-71 For Obviousness-Type Double Patenting (Item 6 of Office Action)

Claims 15, 17, 59-60 and 62-71 have been rejected under the doctrine of obviousness-type double patenting. It is said that the rejected claims are "unpatentable over claims 1-65 (especially claims 1, 18-24, 30, 36-42, 48 and 54-60) of U.S. Patent No. 6,471,978 alone or in combination with its disclosure (e.g., col. 1-4) for purposes of demonstrating inherency." The Examiner is requested to clarify how the disclosure is being used and exactly what is said to be inherent, in reference to specific claims.

The Examiner has not set forth the rejection with sufficient particularity that Applicants can be expected to understand how each of Claims 15, 17, 59, 60 and 62-71 are not patentably distinct from each of the 65 claims of the patent. The Examiner has given, in effect, 910 bases for rejection in concluding that the rejected claims are unpatentable over Claims 1-65 of US Patent No. 6,471,978.

Section 804 of the MPEP gives guidance on determining whether a nonstatutory basis exists for a double patenting rejection. Page 800-22 of the MPEP (8th edition, revised February, 2003) states:

> Any obviousness-type double patenting rejection should make clear:
>
> (A) The differences between the inventions defined by the conflicting claims -- a claim in the patent compared to a claim in the application; and

> (B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent.

The Examiner has not made clear the differences between each of the rejected claims and each of the 65 claims of US Patent No. 6,471,978 to which each of the rejected claims are being compared, and the reasons why a person of ordinary skill in the art would conclude that the invention defined in each of rejected Claims 15, 17, 59, 60 and 62-71 is an obvious variation of the invention defined in each of Claims 1-65 of the patent. The Examiner instead includes a general discussion of the teachings of the patent, not an analysis of the claims.

The Examiner discusses an interpretation of the teachings of Stamler *et al.* (US 6,471,978) in columns 1-4. The Examiner is requested to clarify how this is being applied to the rejection. Which claim or claims of US 6,471,978 are supported by the disclosure in columns 1-4, and to which claim or claims of the subject patent application is this relevant? Treating the cited patent as prior art is impermissible. In re Kaplan 229 USPQ 678, 683 (CAFC 1986).

The Examiner seems to conclude that one of ordinary skill in the art could extrapolate from the claims of US 6,471,978 that the derivatives of hemoglobin recited in Claims 15, 17, 59, 60 and 62-71 should be administered to an animal or a human for the purpose of inhibiting platelet aggregation. The method of Claims 1-65 is narrow in scope, requiring a damaged vascular surface. The method of Claims 15, 17, 59, 60 and 62-71 of the subject patent application is broad, not requiring the presence of damaged vascular surface for the hemoglobin derivatives to be applied. The class of agents in Claims 1-65 of US 6,471,978 is extremely broad and includes compounds with no demonstrated ability to release NO. It is not true, as the Examiner states, that "the same protein is applied in the same way in the same amount."

In all of Claims 1-65 of US Patent No. 6,471,978, the method is to apply to a damaged vascular surface a nitric oxide adduct. In all of the claims of the subject patent application, the method is to administer to an animal or human a composition comprising a nitrosated or nitrated hemoglobin, which may be nitrosylhemoglobin, SNO-Hb(FeIII), polynitrosated hemoglobin, SNO-Hb[Fe(II)] or SNO-methemoglobin.

It is not apparent to one of ordinary skill in the art why agents that must be applied to a damaged vascular surface for the purpose of treating that damaged vascular surface, and are not effective if administered systemically (see Figure 3 and column 28, line 58 to column 29, line 3), would have any effect on platelet aggregation in an animal or human. For this reason, Claims 15, 17, 59, 60 and 62-71 of the subject patent application are distinct from all the claims of US 6,471,978, and Claims 15, 17, 59, 60 and 62-71 of the subject patent application are not obvious variations of the subject matter of the claims of US 6,471,978.

The Examiner states, "The selection of 'nitric oxide adducts' of hemoglobin (e.g. (S) nitrosated/nitrated polynitrosated) is anticipated or in the alternative obvious since hemoglobin is a preferred (e.g. claimed embodiment)." The Examiner is requested to clarify this statement. To which claim of the application does it refer, and to which claim of the cited patent does it refer? What meaning does "is anticipated or in the alternative obvious" have in the context of an obviousness-type double patenting rejection? The case referred to [*In re Schaumann*, 197 USPQ 5 (CCPA 1978)] has as its issue the question of whether the disclosure of a chemical genus may ever constitute a description of a specific compound falling within the ambit of the genus. The court concluded that the claimed species was obvious in view of the small recognizable class of compounds disclosed in the prior art reference, under 35 U.S.C. § 102(b). Applicants do not see the relevance of *In re Schaumann.* The claims of US 6,471,978 do not include any well-defined chemical genus.

The Examiner states, "Accordingly, the reference teaches treating (humans/animals) disorders resulting from platelet activation or adherence within the scope of the presently claimed invention (e.g. damaged vasculature) which inherently preventing thrombus formation and platelet activation." Treating an animal or human disorder resulting from platelet activation or adherence is not within any of the embodiments of any of the claims of US 6,471,978. The cited teachings are not appropriately used in this double patenting rejection. Treating the cited patent as prior art is impermissible. In re Kaplan 229 USPQ 678, 683 (CAFC 1986).

Rejection of Claims 15-17 and 59-71 For Obviousness-Type Double Patenting (Item 7 of Office Action)

Claims 15-17 and 59-71 have been rejected under the doctrine of obviousness-type double patenting, "as being unpatentable over claims 1-4 of US Patent No. 6,583,113 alone or in combination with its disclosure (e.g. col. 1-4; examples) for purposes of interpreting claim scope and/or demonstrating inherency."

Claims 1-4 of US 6,583,113 are methods comprising delivering nitric oxide to a targeted site in the body of a patient from a nitrosated and/or nitrosylated heme protein, wherein the heme protein is nitrosated and/or nitrosylated at one or more thiol groups in the heme protein. Claim 1 encompasses "treating or preventing a disease or disorder in a patient." However, the meaning and scope of Claims 1-4 are unclear, because it is not required that any treatment be performed on the patient, for example, administering a pharmaceutical substance. Claims 1-4 of US 6,583,113 do not comprise a step of administering to a human a composition comprising a nitrosated or nitrated hemoglobin, which may be nitrosylhemoglobin, SNO-Hb(FeIII), polynitrosated hemoglobin, SNO-Hb[Fe(II)] or SNO-methemoglobin. Because the step of the method is different, Claims 1-17 and 59-71 are patentably distinct from Claims 1-4 of 6,583,113. Claims 1-4 of US 6,583,113 read on a process that occurs in nature, as SNO-hemoglobin, which delivers nitric oxide to sites in the body, occurs naturally in red blood cells. See Table 2 on page 66 of the specification.

The content of US 6,583,113 is the same as that of WO 93/09806, with the exception of the claims. Applicants wish to remind the Examiner that a telephonic interview was held on February 13, 2001, in which the attorney Carol Egner and the inventor Jonathan Stamler discussed issues with the Examiner, Bennett Celsa. Based on the Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 filed on 2 September 1999 and exhibits accompanying the Declaration, the Examiner stated that he accepted that WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin. The Examiner voiced a question of whether other species of nitrosated hemoglobin could have been produced from methods described in WO 93/09806. It was presented to the Examiner that it would be very unlikely that NO adducts were produced at O, N or C atoms in the hemoglobin molecule, if none could be detected at S atoms, because the thiol groups were the most reactive nucleophilic sites.

WO 93/09806 does not present a method to use nitrosylhemoglobin as a donor of NO in therapy. Before the invention by Applicants, nitrosylhemoglobin would not have been expected to be, or to be converted to, a donor of NO. WO 93/09806, and therefore, US 6,583,113 do not present an enabling description of any method to make a nitrosated hemoglobin or a method to use any nitrosated hemoglobin in therapy.

The parent application to US 6,583,113 is 09/092,622 (now US Patent No. 291,424). Applicants request that the Examiner consider the file history of the parent application to the cited patent US 6,583,113. The inventors listed on the face of US 6,291,424 are Johnathan (sic) Stamler, Joseph Loscalzo and David J. Singel. The United States Patent and Trademark Office erred in listing Jonathan Stamler as an inventor. 37 C.F.R. § 1.63 requires, *inter alia*:

> (a) An oath or declaration filed under § 1.51(b)(2) as a part of a nonprovisional application must:
>
> (4) State that the person making the oath or declaration believes the named inventor or inventors to be the original and first inventor or inventors of the subject matter which is claimed and for which a patent is sought.

The file history of US 6,291,424 (specifically, papers submitted as exhibits with a Petition Under 37 C.F.R. § 1.47(a) and Declarations in Support of Filing Under 37 C.F.R. § 1.47(a) filed on December 30, 1998 for 09/092,622) shows that Dr. Stamler did not sign a Declaration of Inventorship for that application because he did not believe the named inventors to be the original and first inventors of the subject matter claimed in the application. See Exhibit P, a copy of "Declaration of Gretchen A. Rice in Support of Filing Under 37 C.F.R. § 1.47(a)" mailed to the United States Patent and Trademark Office on 30 December 1998 for Patent Application No. 09/092,622. Also see Exhibit Q (referred to as Exhibit G in the Declaration of Gretchen A. Rice) a copy of a letter from Maxim H. Waldbaum, Esq. of Sidley & Austin to Gretchen A. Rice, Esq., attorney of record for Patent Application No. 09/092,622. However, in spite of the requirements of 37 C.F.R. § 1.63, the United States Patent and Trademark Office granted the Petition and granted the application Rule 1.47(a) status.

The Senior Legal Advisor who drafted the Decision on the Petition was apparently persuaded by the argument made by the attorney for applicants of 09/092,622 that its

specification "is identical to the specification of USSN 07/943,835." Apparently, the attorney for applicants of 09/092,622 was referring to the written sections of the application excluding the claims. The claims are in fact part of the specification. Therefore, it is not true that the specification of the patent application that became US 6,292,424 is identical to the specification of its parent application, 07/943,835.

The attorney for applicants of 09/092,622 brought up repeatedly in the Declaration in Support of Filing Under 37 C.F.R. § 1.47(a) the fact that Dr. Stamler had previously executed an assignment to Brigham and Women's Hospital for US Patent Application No. 07/943,835 in 1992. However, 37 C.F.R. § 1.63 does not recognize, and no other statute in patent law recognizes any obligation that allegedly results from the signing of an assignment in a related application. Note that 37 C.F.R. § 1.63(a)(4) requires that all named inventors believe the named inventors to be the original and first inventors "*of the subject matter which is claimed and for which a patent is sought.*" The subject matter of the claims in 09/092,622 was different from the subject matter of the claims of prior applications. It should be noted that Application No. 09/092,622 (US 6,291,424) is listed on the face of the 6,291,424 patent as being a continuation-in-part of Application No. 08/409,720 (filed March 24, 1995), which is a continuation-in-part of 08/198,854 (filed February 17, 1994), which is a divisional of 07/943,835 (filed September 14, 1992). The filing of 09/092,622 as a continuation-in-part rather than a continuation application is an acknowledgment that its claims are different from those of previously filed applications to which it claims priority. The signing of the assignment in 07/943,835 should not carry any weight; it does not state anything about the signatory's belief as to who invented the subject matter of the claims.

Copies of the papers in the parent application 09/092,622 -- the Petition Under 37 C.F.R. § 1.47(a), Declarations in Support of Filing Under 37 C.F.R. § 1.47(a) and exhibits accompanying the Declarations -- were submitted with Patent Application No. 09/835,038 (US Patent No. 6,583,113) upon its filing on April 16, 2001. Status as an application under 37 C.F.R. § 1.47(a) was again granted by the Patent Office to 09/835,038, thereby repeating the mistake in the parent application 09/092,622.

Because Jonathan S. Stamler is not an inventor of Claims 1-4 of US Patent No. 6,583,113, there is no common inventor between the instant application and US Patent No. 6,583,113, and no double patenting rejection can apply.

Rejection of Claims 15-17 and 59-71 For Obviousness-Type Double Patenting (Item 8 of Office Action)

Claims 15-17 and 59-71 have been rejected under the doctrine of obviousness-type double patenting, "as being unpatentable over claims 1-17 of copending Application No. 10/216,865 (PG Pub. US 2003/0007967) to Stamler *et al.* alone or in combination with its disclosure (e.g. col. 1-4; examples) for purposes of interpreting claim scope and/or demonstrating inherency." The Examiner is requested to clarify how the disclosure is being used and exactly what is said to be inherent, in reference to specific claims.

The Examiner has not set forth the rejection with sufficient particularity that Applicants can be expected to understand how it is alleged that each of Claims 15-17 and 59-71 are not patentably distinct from each of Claims 1-17 of copending Application No. 10/261,865. The Examiner has given, in effect, 272 bases for rejection in concluding that the rejected claims are unpatentable over Claims 1-17 of copending Application No. 10/216,865.

Section 804 of the MPEP gives guidance on determining whether a nonstatutory basis exists for a double patenting rejection. Page 800-22 of the MPEP (8th edition, revised February, 2003) states:

> Any obviousness-type double patenting rejection should make clear:
>
> (A) The differences between the inventions defined by the conflicting claims -- a claim in the patent compared to a claim in the application; and
>
> (B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent.

The Examiner has not made clear the differences between each of the rejected claims and each of the 17 claims of copending Application No. 10/216,865 to which each of the rejected claims are being compared, and the reasons why a person of ordinary skill in the art would conclude that the

invention defined in each of rejected Claims 15-17 and 59-71 is an obvious variation of the invention defined in each of claims 1-17 of copending Application No. 10/216,865. The Examiner instead includes one sentence that states a conclusion, rather than an analysis of the claims.

The claims of copending Application No. 10/216,865 (PG Pub. US 2003/0007967) to Stamler *et al.*, alone, or in combination with the specification, or in combination with anything else available before the priority date of the subject application, do not enable one of ordinary skill in the art to make and use the invention as claimed in Application No. 10/216,865.

The teachings of Stamler *et al.* in Application No. 10/216,865 (PG Pub. US 2003/0007967) are those of WO 93/09806, with the exception of the claims. Applicants wish to remind the Examiner of his stated conclusion in a telephonic interview in which he discussed issues with attorney Carol Egner and inventor Jonathan Stamler on 13 February 2001. The Examiner stated, that based on the Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 filed on 2 September 1999 and exhibits accompanying the Declaration, he had accepted that WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin.

In this case, there can be no conception without reduction to practice. That is, one might think that a hemoglobin molecule with NO adduct(s) on one or more thiols of the cysteine residues might be possible in theory. However, carrying out any chemical modification on a protein is difficult to do without denaturing the protein, and particularly difficult on a protein that must maintain exact conformations to be able to bind and unload oxygen from the heme in response to the appropriate environmental conditions. There was no demonstration in WO 93/09806 or in Application No. 10/216,865 (PG Pub. US 2003/0007967) that any amount of SNO-hemoglobin was ever produced. Therefore, there was no invention of SNO-hemoglobin by the people named as inventors on Application No. 10/216,865 (PG Pub. US 2003/0007967).

Jonathan S. Stamler has not signed a Declaration of Inventorship in US Patent Application No. 10/216,865 (PG Pub. US 2003/0007967) because he is not an inventor. Because Jonathan S. Stamler is not an inventor of Claims 1-17 of US Patent Application No. 10/216,865, there is no common inventor between the instant application and US Patent Application No. 10/216,865, and no double patenting rejection can apply.

CONCLUSION

The Examiner is requested to consider the above remarks, and to withdraw the rejections. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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